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Standard Commodity Classification No. of Japan
875200

■96■

- Kampo-preparation-

TSUMURA Saibokuto Extract Granules for Ethical Use

Storage
Store in light-resistant, air-tight containers.

Approval No.	(61AM)3272
Date of listing in the NHI reimbursement price	October 1986
Date of initial marketing in Japan	October 1986

Expiration date
Use before the expiration date indicated on the container and the outer package.

DESCRIPTION

Composition	7.5 g of TSUMURA Saibokuto extract granules (hereafter TJ-96) contains 5.0 g of a dried extract of the following mixed crude drugs.	
		JP Bupleurum Root 7.0 g JP Pinellia Tuber..... 5.0 g JP Poria Sclerotium 5.0 g JP Scutellaria Root 3.0 g JP Magnolia Bark 3.0 g JP Jujube 3.0 g JP Ginseng 3.0 g JP Glycyrrhiza 2.0 g JP Perilla Herb 2.0 g JP Ginger 1.0 g (JP : The Japanese Pharmacopoeia)
	Inactive ingredients	JP Magnesium Stearate JP Lactose Sucrose Esters of Fatty Acids
Description	Dosage form	Granules
	Color	Light brown
	Smell	Characteristic smell
	Taste	Slightly sweet and astringent
	ID code	TSUMURA/96

PRECAUTIONS

1. Careful Administration (TJ-96 should be administered with care in the following patients.)

Patients with greatly declined constitution [Adverse reactions are likely to occur, and the symptoms may be aggravated.]

2. Important Precautions

- When TJ-96 is used, the patient's "SHO" (constitution/symptoms) should be taken into account. The patient's progress should be carefully monitored, and if no improvement in symptoms/findings is observed, continuous treatment should be avoided.
- Since TJ-96 contains Glycyrrhiza, careful attention should be paid to the serum potassium level, blood pressure, etc., and if any abnormality is observed, administration should be discontinued.
- When TJ-96 is coadministered with other Kampo-preparations (Japanese traditional herbal medicines), etc., attention should be paid to the duplication of the contained crude drugs.

SHO: The term "SHO" refers to a particular pathological status of a patient evaluated by the Kampo diagnosis, and is patterned according to the patient's constitution, symptoms, etc. Kampo-preparations (Japanese traditional herbal medicines) should be used after confirmation that it is suitable for the identified "SHO" of the patient.

INDICATIONS

TJ-96 is indicated for the relief of the following symptoms of those patients who have depressed feelings and a feeling of foreign body in the throat and oesophagus and who sometimes have palpitation, dizziness, nausea, etc.:

Infantile asthma, bronchial asthma, bronchitis, coughing, and anxiety neurosis

DOSAGE AND ADMINISTRATION

The usual adult dose is 7.5 g/day orally in 2 or 3 divided doses before or between meals. The dosage may be adjusted according to the patient's age and body weight, and symptoms.

3. Drug Interactions

Precautions for coadministration (TJ-96 should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
(1) Preparations containing Glycyrrhiza (2) Preparations containing glycyrrhizinic acid or glycyrrhizines	Pseudoaldosteronism is likely to occur. Besides, myopathy is likely to occur as a result of hypokalemia. (Refer to the section "Clinically significant adverse reactions".)	Since glycyrrhizinic acid has an accelerating action on the potassium excretion at the renal tubules, an acceleration of decrease in the serum potassium level has been suggested.

4. Adverse Reactions

TJ-96 has not been investigated (drug use investigations, etc.) to determine the incidence of adverse reactions. Therefore, the incidence of adverse reactions is not known.

(1) Clinically significant adverse reactions

- 1) Interstitial pneumonia:** If fever, cough, dyspnea, abnormal pulmonary sound (fine crackle), etc. are observed, administration of TJ-96 should be discontinued, and examinations such as X-ray should be performed immediately and appropriate measures such as administration of adrenocortical hormones taken. Besides, the patient should be advised to discontinue TJ-96 immediately and to make contact with the physician in the event of fever, cough, dyspnea, etc.
- 2) Pseudoaldosteronism:** Pseudoaldosteronism such as hypokalemia, increased blood pressure, retention of sodium/body fluid, edema, increased body weight, etc. may occur. The patient should be carefully monitored (measurement of serum potassium level, etc.), and if any abnormality is observed, administration should be discontinued and appropriate measures such as administration of potassium preparations should be taken.
- 3) Myopathy:** Myopathy may occur as a result of hypokalemia. The patient should be carefully monitored, and if any abnormality such as weakness, convulsion/paralysis of limbs, etc. are observed, administration should be discontinued and appropriate measures such as administration of potassium preparations should be taken.
- 4) Hepatic dysfunction and jaundice:** Hepatic dysfunction and/or jaundice with remarkable elevation of AST (GOT), ALT (GPT), ALP and γ -GTP or other symptoms may occur. The patient should be carefully monitored for abnormal findings. Administration should be discontinued and appropriate therapeutic measures should be taken, if abnormalities are observed.

(2) Other adverse reactions

	Incidence unknown
Hypersensitivity ^{note1)}	Rash, Urticaria, etc.
Gastrointestinal	Dry mouth, Anorexia, Epigastric distress, Abdominal pain, Diarrhea, Constipation, etc.
Urinary ^{note2)}	Pollakiuria, Micturition pain, Hematuria, Feeling of residual urine, Cystitis, etc.

Note

- 1) In the event of such symptoms, administration should be discontinued.
- 2) Since these symptoms may occur. The patient should be carefully monitored, and if abnormalities are observed, administration of the drug should be discontinued and appropriate therapeutic measures taken.

5. Use in the Elderly

Because elderly patients often have reduced physiological function, careful supervision and measures such as reducing the dose are recommended.

6. Use during Pregnancy, Delivery or Lactation

Use of TJ-96 in pregnant women, women who may possibly be pregnant is not recommended.

7. Pediatric Use

The safety of TJ-96 in children has not been established. [Insufficient clinical data]

8. Other Precautions

Adverse reactions of interstitial pneumonia, liver dysfunction and cystitis have been reported with a similar prescription "Shosaikoto". In particular, interstitial pneumonia has been reported frequently in the case of combined use with interferon- α .

PHARMACOLOGY

1. Anti-inflammatory actions

- (1) Oral administration of Saibokuto to a guinea pig ovalbumin-sensitized asthma model suppressed antigen-induced airway hyperreactivity and eosinophil accumulation¹⁾.
- (2) Oral administration of Saibokuto to a guinea pig ovalbumin-sensitized dual-phase asthma models inhibited late asthmatic response (LAR). Furthermore, Saibokuto inhibited increases in the cell counts (eosinophil, neutrophil, macrophage, and lymphocyte counts) in the LAR (4 h after antigen challenge), but not in the immediate response (10 min after antigen challenge) and also inhibited T-lymphocyte infiltration²⁾.
- (3) Oral administration of Saibokuto to Ascaris antigen-sensitized guinea pigs inhibited the enhancement of respiratory resistance related to late asthmatic response. Furthermore, Saibokuto decreased the bronchoalveolar lavage level of histamine, and inhibited lung tissue infiltration of eosinophils/granulocytes³⁾.
- (4) In canine bronchial smooth muscle, Saibokuto augmented the isoproterenol-induced relaxant response of the tissue precontracted with acetylcholine. Saibokuto did not affect cyclic AMP levels in airway smooth muscle per se but

potentiated the isoproterenol-induced cyclic AMP accumulation (*in vitro*)⁴

2. Improvement of airway epithelium mucociliary transport

In rabbit tracheal mucosal epithelial cells, Saibokuto enhanced ciliary movement, and increased the level of cyclic AMP (*in vitro*)⁵.

3. Anxiolytic actions (Anxiolytic-like effects)

(1) Oral administration of Saibokuto to mice showed anxiolytic-like effects in an improved elevated plus-maze test⁶.

(2) Oral administration of Saibokuto to mice showed anxiolytic-like effects in a light/dark test. Saibokuto inhibited cerebral histaminergics-induced behavioral anxiolytic-like related to Compound 48/80 or thioperamide stimulation⁷.

4. Action mechanism

Saibokuto shows pharmacological effects via the following actions:

(1) Inhibition of the production/release of chemical mediators

1) Inhibition of the production of leukotriene (LT)

In rat basophilic leukemia cells, Saibokuto inhibited the production of pLTs (LTC₄, LTD₄, LTE₄) and LTB₄ by retinoic acid and calcium ionophores (*in vitro*)⁸.

2) Inhibition of histamine release

In rat peritoneal mast cells, Saibokuto inhibited Compound 48/80 induced degranulation and histamine release (*in vitro*)⁹.

3) Inhibition of arachidonic acid metabolites

In cultured porcine pulmonary artery endothelial cells, Saibokuto inhibited the production of cyclooxygenase and lipooxygenase derivatives (*in vitro*)¹⁰.

(2) Actions on cytokine production

1) In peripheral blood mononuclear cell from the bronchial asthma patients, Saibokuto inhibited the production of IL-3 and IL-4, however it increased the production of INF- γ (*in vitro*)¹¹.

2) In peripheral blood mononuclear cells derived from patients with severe refractory asthma, Saibokuto inhibited the Candida stimulation induced production of IL-2 and the expression of IL-2 receptors (*in vitro*)¹².

(3) Actions on eosinophils

Saibokuto inhibited IL-3, IL-5 and GM-CSF (granulocyte macrophage colony stimulating factor) induced prolongation of eosinophils (*in vitro*)¹³.

(4) Actions on NO generation

In canine airway epithelial cells, Saibokuto increased the production of NO involved in the enhancement of airway movement (*in vitro*)¹⁴.

(5) Inhibitory effects on the expression of adhesion molecules

In human eosinophils, Saibokuto did not inhibit the expression of CD54 and HLA-DR. However, Saibokuto down-regulated CD4 expression¹⁵.

PACKAGING

Bottles of 500 g and boxes of 5 kg (500 g \times 10 bottles)

2.5 g \times 42 packets

2.5 g \times 189 packets

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